and wherein the antibody specifically binds to at least one polypeptide selected from the group consisting of the human adenine nucleotide translocator polypeptide, the DLYDDDDK [SEQ ID NO:56] epitope tag and the DYKDDDDK [SEQ ID NO:55] epitope tag.

REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendment and the following remarks. Claims 92-139 are pending in the application, with claims 109-139 standing withdrawn from consideration by the Examiner, without prejudice to prosecution in a related application. Accordingly, claims 92-108 are currently under examination in the application, with claims 92-107 standing rejected, and claim 108 objected to as being dependent upon a rejected base claim, but being otherwise allowable if rewritten in independent form. By the above amendment, claim 107 has been amended, for purposes of clarity and to more particularly set forth Applicants' claimed invention. The amendment and remarks provided herein are not to be construed as acquiescence with regard to the Examiner's rejections, and are made without prejudice to prosecution of Applicants' disclosed subject matter in a related divisional, continuation and/or continuation-in-part application. For the Examiner's convenience, please find appended hereto a complete set of the currently pending claims.

REQUEST FOR WITHDRAWAL OF FINALITY OF OFFICE ACTION DATED OCTOBER 21, 2002

As an initial matter, Applicants respectfully request reconsideration and withdrawal of the finality of the Office Action dated October 21, 2002; as elaborated upon hereinbelow, Applicants believe the final rejection is premature.

> If, on request by applicant for reconsideration, the primary examiner finds the final rejection to have been premature, he or she should withdraw the finality of the rejection. The finality of the Office action must be withdrawn while the application is still pending. (MPEP 706.07(d))

Applicants respectfully submit that the Final Office Action dated October 21, 2002, by failing to substantively consider and address Applicants' Response filed July 30, 2002, is premature in its finality. More particularly, in the Response filed July 30, 2002, Applicants noted and questioned why the apparent basis for the Examiner's rejections under 35 U.S.C. § 103 relied on alleged teachings of the cited art pertaining to "first energy transfer molecules", "second energy transfer molecules", "MPT" (mitochondrial permeability transition), and the like,

when these terms and concepts are, in fact, unrelated to the claimed subject matter currently under examination.

Despite Applicants' request for clarification on these points in the Response filed July 30, 2002, however, the Office Action dated October 21, 2002, maintained identical rejections under 35 U.S.C. § 103, devoid of additional explanation or clarification as to how teachings of Marban *et al.*, Luban *et al.* and Anderson *et al.* that allegedly relate to "MPT" and "energy transfer molecules" can render obvious Applicants' presently claimed invention, when these terms, concepts and limitations that the Examiner alleges are taught by the cited art bear no substantive relationship to the currently claimed subject matter. Rather, the Final Office Action dated October 21, 2002, reiterated the very same arguments made in the First Office Action dated January 30, 2002, offering in reply to Applicants' questions and requests for clarification only that "one cannot show nonobviousness by attacking references individually where a rejection is based on a combination of references", without offering any additional substantive clarification as to the scientific basis upon which the rejections were predicated.

The claims under consideration in the instant application simply and unequivocally do not recite, nor are they expressly directed to, "MPT" or "energy transfer." Accordingly, on the basis of the Examiner's reliance on cited references for their asserted teachings of claim terms and limitations that are not recited or embodied by the claims currently under examination, and further on the basis of the lack of any substantive reply to Applicants' arguments and requests for clarification as made of record in the Response filed on July 30, 2002, Applicants respectfully request that the finality of the Office Action dated October 21, 2002, be reconsidered by the Primary Examiner, and, if the finality is deemed premature, that a new Action on the merits be provided to Applicants.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 107 remains rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. More particularly, it is alleged that claim 107 uses the trademarks "XPRESS" and "FLAG" to identify or describe polypeptide tags of uncertain scope, rendering these recitations indefinite.

Applicants respectfully traverse this rejection and submit that the rejection is moot in view of the present amendment. The trademarks recited in claim 107 (FLAG® and XPRESS™) have been deleted and replaced with actual epitope tag amino acid sequences DYKDDDDK (SEQ ID NO:55) and DLYDDDDK (SEQ ID NO:56), respectively (*see, e.g.*, specification at page 28, line 24 through page 29, line 5; at page 70, lines 3-10; at page 82, lines 2-4; at page 83, lines 22-27; at page 87, lines 1-2; page 102, lines 6-11; at page 117, lines 20-23). As already established in Applicants' Response filed July 30, 2002, Applicants respectfully submit that amendment of the instant specification and claims to include amino acid sequences for the FLAG® and XPRESS™ epitope tags is proper and does not add new matter, because the peptide epitope sequences were disclosed in the references cited by the specification (for FLAG® [SEQ ID NO: 55], see, *e.g.*, U.S. 5,011,912 and Hopp *et al.*, 1988 *BioTechnol.* 6:1204, cited, *e.g.*, at specification page 28, lines 27-29; for XPRESS™ [SEQ ID NO:56], see, *e.g.*, "pBAD/His", the unique identifier for a vector, the map and sequence of which are available from Invitrogen, Carlsbad, CA, (a manufacturer well known to the art) and which are described in catalogs of this supplier, cited, *e.g.*, at specification page 87, line 2), which publications are incorporated by reference in the instant specification (*e.g.*, at page 15, lines 14-17). Moreover, FLAG® and XPRESS™ epitope tags were available on the market and were known generally to those having ordinary skill in the art of molecular biology, and had a fixed and definite meaning at the time the subject application was filed (see, *e.g.*, *In re Gebauer-Fuelnegg*, 50 U.S.P.Q. 125, 128, C.C.P.A. 1941).

Accordingly, Applicants submit that claim 107 satisfies the requirements of 35 U.S.C. § 112, second paragraph, and respectfully request that this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

A. Claims 92-94, 97-103 and 105 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Marban *et al.* (U.S. Patent No. 6,183,948), in view of Luban *et al.* (U.S. Patent No. 5,773,225), and further in view of Anderson *et al.* (U.S. Patent No. 6,140,067).

Applicants respectfully traverse this rejection for reasons already made of record by Applicants and further in view of the comments provided below.

This rejection is essentially identical to that made in the First Office Action dated January 30, 2002. In particular, the Action continues to allege that Marban *et al.* teach a screening assay for an agent that alters mitochondrial permeability transition (MPT) comprising steps that include contacting a host cell with a candidate agent and an inducer of MPT, exposing the cell to excitation energy, detecting energy transfer (ET) between first and second ET molecules and comparing the energy transfer level to a reference level generated in the absence of candidate agent.

However, as set forth previously by Applicants, and as further discussed herein, the instant claims neither recite nor embody "MPT" or "energy transfer."

The Action asserts that Luban *et al.* teach a method wherein the host cell comprises a first nucleic acid expression construct comprising a promoter operably linked to a polynucleotide encoding a first ET molecule and a second nucleic acid expression construct comprising a promoter operably linked to a polynucleotide encoding a cyclophilin polypeptide fused to a second ET molecule. The Examiner alleges further that in the method of Luban *et al.*, "binding of the polypeptide to the cyclophilin polypeptide results in detectable energy transfer between the first and second energy transfer molecules (Figures 1-2 and Column 6, line 40 to column 9, line 25)".

However, as noted above, the instant claims under examination in this application neither recite nor embody a "first ET molecule", a "second ET molecule", or "detectable energy transfer between the first and second energy transfer molecules."

The Action also asserts that Anderson *et al.* teach detection of agents that alter MPT, ANT-cyclophilin binding in mitochondrial membranes, comparing altered mitochondrial function in the presence and absence of a candidate agent, a method for altering cell survival, and a nucleotide construct encoding a MPT pore component polypeptide fused to a polynucleotide wherein binding of the MPT pore component polypeptide to the cyclophilin polypeptide results in detectable energy transfer between first and second ET molecules. The Action then alleges that a person having ordinary skill in the art would have found it obvious to substitute the MPT pore component polypeptide of Anderson *et al.* in the screening method of Marban *et al.* modified in view of Luban *et al.*

Applicants respectfully again point out that the instant claims under consideration in this application neither recite nor embody "MPT", "energy transfer", or detectable energy transfer between first and second energy transfer molecules.

Rather, the claims under examination in this application relate to methods comprising the combination of using (i) an isolated recombinant cyclophilin polypeptide, and (ii) a sample comprising an isolated recombinant adenine nucleotide translocator (ANT) polypeptide, in a binding assay to screen for agents that increase or decrease binding between the two types of recombinant polypeptides. The references cited by the Action, alone or in combination, fail to teach or in any way suggest the recited step of contacting an isolated *recombinant cyclophilin polypeptide* and an isolated *recombinant ANT polypeptide*, in the absence and presence of a candidate agent, in a method of identifying an agent that alters ANT-cyclophilin binding.

Marban *et al.* merely disclose excitation and detection of endogenous cellular flavoprotein fluorescence as a mitochondrial redox marker, or of the fluorescence emission of a cellularly introduced fluorescent marker such as TMRE (Col. 14, lines 16-28, 39-42, 45-57). However, Marban *et al.* fail to teach or suggest any recombinant cyclophilin polypeptide, Marban *et al.* fail to teach or suggest any recombinant ANT polypeptide, and Marban *et al.* fail to teach or suggest a binding interaction between these two types of polypeptides in any manner, much less in a manner that could be viewed as rendering obvious Applicants' presently claimed screening methods. Neither do Marban *et al.* in any way suggest the desirability of combining any teachings found therein with the teachings of Luban *et al.* and/or of Anderson *et al.*, to arrive at the present invention.

Luban *et al.* describe one specific application of the well known yeast two-hybrid screening system for identifying interacting gene products, detected by colorimetric determination of the reporter gene product beta-galactosidase-mediated conversion of the β-galactosidase (β-Gal) substrate X-Gal, to identify HIV gag protein binding to cyclophilin A or cyclophilin B. While Luban *et al.* discuss an interaction between cyclophilin A and HIV gag, Luban *et al.*, whether alone or in combination with the disclosures of Marban *et al.* and/or of Anderson *et al.*, fail to teach or suggest an interaction between a recombinant cyclophilin polypeptide and a recombinant ANT polypeptide in any manner, much less in a manner that would render obvious the currently claimed screening methods. Neither do Luban *et al.* in any

way suggest the desirability of combining any teachings found therein with the teachings of Marban *et al.* and/or of Anderson *et al.*, to arrive at the present invention.

Anderson *et al.* disclose diagnostic and screening methods for type 2 diabetes by comparing levels of one or more indicators of altered mitochondrial function. Certain indicators of mitochondrial function are disclosed as being represented by mitochondrial membrane components, including ANT and CypD, among others. In this regard, Applicants respectfully note that, contrary to the Examiner's assertion in the Action, nowhere do Anderson *et al.* teach or suggest cyclophilin D polypeptides and ANT polypeptides as mitochondrial membrane components "which can naturally interact and bind to each other (Claim 23 and 91 and Column 3, lines 49-62)."(Action, page 6) Rather, these claims and passages of Anderson *et al.* that are referenced by the Examiner merely disclose that cyclophilin D and ANT are among a list of illustrative "indicators of altered mitochondrial function", not that cyclophilin D and ANT polypeptides naturally interact and bind to each other. Neither do Anderson *et al.* teach or suggest the presently claimed method comprising contacting isolated *recombinant* ANT and isolated *recombinant* cyclophilin polypeptides, nor do Anderson *et al.* in any way suggest the desirability of combining any teachings found therein with the teachings of Marban *et al.* and/or of Luban *et al.*, to arrive at the present invention.

Applicants therefore respectfully submit that the cited art publications, either alone or in combination, cannot be fairly viewed as rendering obvious the claimed screening methods for identifying agents that increase or decrease binding between a recombinant cyclophilin polypeptide and a sample comprising a recombinant ANT polypeptide, when the cited art fails to teach, suggest or remotely contemplate even the existence of a possible binding interaction between these two types of proteins.

Reconsideration and withdrawal of this rejection under 35 U.S.C. § 103 is thus respectfully requested.

B. The Action also maintains the previous rejection of claims 92-94 and 96-105 under 35 U.S.C. § 103 over Marban *et al.*, in view of Luban *et al.*, further in view of Anderson *et al.*, and further in view of Briggs *et al.* (U.S. 6,211,440). Specifically, Briggs *et al.* are cited on the basis that they allegedly teach "energy transfer" molecules that are green fluorescent proteins (GFP).

Applicants respectfully traverse the this rejection for reasons already made of record by Applicants, and as further discussed herein.

The deficiencies of the combination of Marban *et al.*, Luban *et al.* and Anderson *et al.*, as discussed above, are equally applicable in the context of the instant rejection. These deficiencies are not remedied by the disclosure by Briggs *et al.* of an alleged "energy transfer" molecule, particularly when "energy transfer" is neither recited nor embodied by the instant claims. Briggs *et al.* simply disclose GFP as one of numerous useful labels for detecting nucleic acids, but the teachings of Briggs *et al.* are irrelevant to the presently claimed screening assay for an agent that alters binding of a recombinant ANT polypeptide to a recombinant cyclophilin polypeptide. Accordingly, Applicants respectfully submit that Briggs *et al.* offer nothing of substance in relation to the currently claimed invention, when viewed in combination with Marban *et al.*, Luban *et al.* and/or Anderson *et al.*, that would lead the artisan of ordinary skill to any method according to the instant claims.

Reconsideration and withdrawal of this rejection is respectfully requested.

C. Claims 92-95, 97-103 and 105-106 stand rejected under 35 U.S.C. § 103 over Marban *et al.* in view of Luban *et al.*, further in view of Anderson *et al.*, and further in view of Halestrap *et al.* (1998 *Biochim. Biophys. Acta.* 1366:79). The assertions in the Action with respect to Marban *et al.*, in view of Luban *et al.*, and further in view of Anderson *et al.*, are described above. The Action asserts further that Halestrap *et al.* teach the claimed method wherein cyclophilin A polypeptide is used (claim 95), and wherein the detection reagent is an antibody (claim 106).

Applicants respectfully traverse this rejection for reasons already made of record, and as further discussed herein.

The deficiencies already noted with respect to the combination of Marban *et al.*, Luban *et al.* and Anderson *et al.* are equally applicable in the context of this rejection. More specifically, this combination of references fails to teach or remotely suggest even the possibility of a binding interaction between a cyclophilin polypeptide and an ANT polypeptide, much less between (i) an isolated recombinant cyclophilin polypeptide and (ii) a sample comprising an isolated recombinant adenine nucleotide translocator (ANT) polypeptide, in a binding assay to

screen for agents that increase or decrease binding between the two types of recombinant polypeptides, as claimed by Applicants.

Halestrap *et al.* fail to provide any disclosure relating to a binding assay in which a sample comprising an isolated *recombinant* ANT polypeptide binds to an isolated *recombinant* cyclophilin polypeptide, regardless of whether an antibody is used as a detection reagent. On this point, the Action makes specific reference to page 80, section 2.1 of Halestrap *et al.*, but Applicants submit that Halestrap *et al.* therein merely describe assays of cyclophilin A peptidyl-prolyl cis-trans isomerase activity, which neither teaches nor suggests assays of binding between recombinant ANT and recombinant cyclophilin polypeptides. Nowhere do Halestrap *et al.* teach or suggest a direct and straightforward binding assay between a recombinant ANT polypeptide and a recombinant cyclophilin polypeptide, as provided only by the present disclosure. In fact, Halestrap *et al.* disclose only the use of *non-recombinant* ANT from detergent solubilized mitochondrial membranes, and, at most, suggest merely the possibility of a binding interaction between a recombinant cyclophilin fusion protein and a non-recombinant ANT based upon indirect measurements. In other words, doubt is cast on any showing by Halestrap *et al.* of a binding interaction between non-recombinant ANT and recombinant cyclophilin where there is no showing by Halestrap *et al.* of such binding using a recombinant cyclophilin polypeptide having a different fusion domain (*i.e.*, the non-cyclophilin portion), or no fusion domain at all.

Additionally, even assuming *arguendo* that a person having ordinary skill in the art were to find a suggestion by Halestrap *et al.*, alone or in combination with any other cited or contemporaneous reference, that a cyclophilin polypeptide may be capable of binding to a *non-recombinant* ANT polypeptide, and even assuming further for argument's sake that such a skilled artisan were to find motivation to attempt to develop a screening method, according to the claimed invention, for identifying agents that can alter the binding of a recombinant cyclophilin polypeptide to a recombinant ANT polypeptide, Applicants submit that a reasonable expectation of success in developing such a method was clearly lacking prior to Applicants' disclosure.

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success viewed in the light of the prior art...Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Dow Chemical Co.,* 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988)

Moreover, it is axiomatic that an assertion that it would have been "obvious to try" to improve on the prior art methods cannot be regarded as a conclusory finding that the claimed invention is obvious, and fails to support a *prima facie* case of obviousness. *In re Eli Lilly & Co.*, 902 F.2d 943; 14 USPQ2d 1741 (Fed. Cir. 1990). Applicants submit that the Action employs inappropriate and selective hindsight where the allegation of obviousness derives not from a reason or suggestion in the art, but impermissibly from knowledge provided by Applicants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469; 5 USPQ2d 1529 (Fed. Cir. 1988). Applicants therefore respectfully submit that any reasonable expectation of success in practicing the currently claimed screening methods exists only as a result of, and is thus impermissibly founded in, Applicants' own disclosure.

Indeed, numerous factors argue against a reasonable expectation of success finding foundation in the prior art in this instance. For example, it was unpredictable, in view of the cited art, whether one could even successfully generate a recombinant ANT polypeptide, much less use the recombinant ANT in a binding assay in conjunction with a recombinant cyclophilin polypeptide. ANT plays a prominent role in respiratory, metabolic, apoptotic and other processes of the mitochondria, the altered function of which, in turn, is thought to be associated with numerous neurodegenerative diseases. The attention directed to human and animal ANT polypeptides by numerous investigators, and the lack of disclosure of recombinant ANT production in the scientific literature, underscores a recognition by the art of the difficulties associated with recombinant ANT production. The prior art offered no reliable approach for the expression of recombinant ANT despite knowledge of the cDNA sequence encoding human ANT polypeptide, and despite the availability of general recombinant protein expression techniques.

Applicants submit that the skilled artisan would have readily understood, given the failure of others to express a recombinant ANT polypeptide long after ANT encoding polynucleotide sequences had been published, that recombinant expression of an ANT polypeptide was not a routine matter. One example of such failure of others to produce recombinant ANT polypeptide is provided by Miroux *et al.* (*J. Mol. Biol.* 260(3): 289, 1996), wherein multiple problems are described with regard to efforts to express recombinant ANT, including toxicity to host cells, poor solubility of the recombinant protein and accumulation of

recombinant ANT in inclusion bodies; a form amenable neither to ready isolation nor to functional binding interactions with an ANT ligand.

It was also unpredictable, prior to Applicants' disclosure, whether a recombinant ANT polypeptide, once successfully produced, would be capable of binding interactions with a recombinant cyclophilin polypeptide in a manner effective for use in a screening method according to the instant claims.

It was also unpredictable, prior to Applicants' disclosure, whether a recombinant ANT polypeptide, once successfully produced, could be used in the context of a "sample" as currently claimed, while still maintaining its binding interactions with a recombinant cyclophilin in a manner effective for use in a screening method according to the instant claims.

Moreover, and with particular regard to Applicants' claimed embodiments wherein the recombinant cyclophilin polypeptide and the recombinant ANT polypeptide are "fusion" polypeptides, it was also unpredictable, prior to Applicants' disclosure, whether recombinant fusion polypeptides of cyclophilin and ANT would be capable of maintaining their binding interactions and/or enzymatic activities, and, importantly, still be effective for use in a screening method as described and claimed by Applicants.

Further still, with particular respect to Applicants' claimed embodiments wherein the "sample" which comprises the isolated recombinant ANT polypeptide comprises at least one isolated mitochondrion, at least one submitochondrial particle, or is immobilized on a solid support, it was also unpredictable, prior to Applicants' disclosure, whether one could adapt a recombinant ANT polypeptide, once successfully produced, for use in the context of these sample types, while still maintaining necessary binding interactions with a recombinant cyclophilin polypeptide for effective use according to the claimed invention.

Thus, and in light of the foregoing, even to the extent an ordinarily skilled artisan might, for argument's sake, have viewed the cited art as offering a suggestion or motivation to attempt to develop a method embodied by Applicants' claims, there would nevertheless have been no reasonable expectation, founded in the prior art, that the screening methods could have been successfully practiced. Instead, given the variety of factors contributing to the unpredictability of the invention as noted above, it is submitted that only in view of Applicants' disclosure in the present application that the skilled artisan would appreciate any reasonable expectation of success in practicing the currently claimed invention. Accordingly, Applicants

respectfully submit that the cited combination of references fails to support an obviousness rejection of Applicants' claims under 35 U.S.C. § 103.

Reconsideration and withdrawal of the Examiner's rejection is thus respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**" The Commissioner is hereby authorized to charge any fee deficiency, or credit any fee overpayment, to Deposit Account No. 19-1090. All of the claims remaining in the application are believed to be in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Anne N. Murphy *et al.*

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 107 has been amended as set forth below:

107. (Amended) The method of claim 106 wherein the second isolated recombinant polypeptide comprises a human adenine nucleotide translocator polypeptide or variant thereof that is fused to a polypeptide selected from the group consisting of a DLYDDDDK [SEQ ID NO:56] epitope tag and a DYKDDDDK [SEQ ID NO:55] epitope tag, and wherein the antibody specifically binds to at least one polypeptide selected from the group consisting of the human adenine nucleotide translocator polypeptide, the DLYDDDDK [SEQ ID NO:56] ~~XPRESS™~~ epitope tag and the DYKDDDDK [SEQ ID NO:55] ~~FLAG®~~ epitope tag.

APPENDIX: CURRENTLY PENDING CLAIMS

[Proposed Amendment to 107 not added]

92. A method of identifying an agent that alters binding of an adenine nucleotide translocator polypeptide to a cyclophilin polypeptide, comprising:
(a) contacting, in the absence and presence of a candidate agent, (i) a first isolated recombinant polypeptide comprising a cyclophilin polypeptide or variant thereof with (ii) a sample comprising a second isolated recombinant polypeptide that comprises a recombinant human adenine nucleotide translocator polypeptide or variant thereof, under conditions and for a time sufficient to permit the cyclophilin polypeptide, the adenine nucleotide translocator polypeptide and the candidate agent to interact; and
(b) comparing a level of binding of the first isolated recombinant polypeptide to the second isolated recombinant polypeptide in the absence of the candidate agent to the level of binding of the first isolated recombinant polypeptide to the second isolated recombinant polypeptide in the presence of the candidate agent, wherein a decreased level of binding in the presence of the agent indicates an agent that inhibits binding of an adenine nucleotide translocator polypeptide to a cyclophilin polypeptide and wherein an increased level of binding in the presence of the agent indicates an agent that enhances binding of an adenine nucleotide translocator polypeptide to a cyclophilin polypeptide, and therefrom identifying an agent that alters binding of an adenine nucleotide translocator polypeptide to a cyclophilin polypeptide.

93. The method of claim 92 wherein at least one of the first and second isolated recombinant polypeptides is a fusion polypeptide.

94. The method of claim 92 wherein the first isolated recombinant polypeptide comprises a human cyclophilin D polypeptide that is fused to an additional polypeptide, wherein the additional polypeptide is other than glutathione-S-transferase,

95. The method of claim 92 wherein the cyclophilin polypeptide is selected from the group consisting of human cyclophilin A, human cyclophilin B, human cyclophilin C and human Cyp-60.

96. The method of claim 92 wherein the first isolated recombinant polypeptide comprises a cyclophilin polypeptide fused to an additional polypeptide that is selected from the group consisting of polyhistidine, polylysine, a haemagglutinin epitope tag, a DLYDDDDK [SEQ ID NO:56] epitope tag, a DYKDDDDK [SEQ ID NO:55] epitope tag, a Myc epitope polypeptide, a FLASH peptide, an immunoglobulin constant region polypeptide, streptavidin, a green fluorescent protein polypeptide, an aequorin polypeptide, a glutathione-S-transferase polypeptide and a *Staphylococcus aureus* protein A polypeptide.

97. The method of claim 92 wherein the first isolated recombinant polypeptide is detectably labeled with a linked reporter group.

98. The method of claim 92 wherein the first isolated recombinant polypeptide comprises a cyclophilin polypeptide fused to an additional polypeptide that is polylysine and the second isolated recombinant polypeptide comprises a recombinant human adenine nucleotide translocator polypeptide fused to an XPRESS™ epitope tag.

99. The method of claim 98 wherein the first isolated recombinant polypeptide is detectably labeled with a linked reporter group.

100. The method of either claim 97 or claim 99 wherein the linked reporter group is selected from the group consisting of a radioactive reporter group, a dye, an enzyme, a ligand, a receptor, a protease recognition sequence, a luminescent reporter group and a fluorescent reporter group.

101. The method of claim 92 wherein the sample which comprises the second isolated recombinant polypeptide comprises at least one isolated mitochondrion.

102. The method of claim 92 wherein the sample which comprises the second isolated recombinant polypeptide comprises at least one submitochondrial particle.

103. The method of claim 92 wherein the sample which comprises the second isolated recombinant polypeptide is immobilized on a solid support.

104. The method of claim 92 wherein the second isolated recombinant polypeptide comprises a human adenine nucleotide translocator polypeptide or variant thereof that is fused to an additional polypeptide selected from the group consisting of polyhistidine, polylysine, a haemagglutinin epitope tag, a DLYDDDDK [SEQ ID NO:56] epitope tag, a DYKDDDDK [SEQ ID NO:55] epitope tag, a Myc epitope polypeptide, a FLASH peptide, an immunoglobulin constant region polypeptide, streptavidin, a green fluorescent protein polypeptide, an aequorin polypeptide, a glutathione-S-transferase polypeptide and a *Staphylococcus aureus* protein A polypeptide.

105. The method of claim 92 wherein the step of comparing binding levels comprises detection of a detection reagent that specifically binds to at least one of the polypeptides selected from the group consisting of the first isolated recombinant polypeptide and the second isolated recombinant polypeptide.

106. The method of claim 105 wherein the detection reagent is an antibody.

107. The method of claim 106 wherein the second isolated recombinant polypeptide comprises a human adenine nucleotide translocator polypeptide or variant thereof that is fused to a polypeptide selected from the group consisting of a DLYDDDDK [SEQ ID NO:56] epitope tag and a DYKDDDDK [SEQ ID NO:55] epitope tag, and wherein the antibody specifically binds to at least one polypeptide selected from the group consisting of the human adenine nucleotide translocator polypeptide, the XPRESS™ epitope tag and the FLAG® epitope tag.

108. The method of claim 92 wherein the first isolated recombinant polypeptide comprises human cyclophilin D and wherein the sample which comprises the second isolated recombinant

polypeptide comprises at least one submitochondrial particle isolated from a *T. ni* cell that expresses a recombinant human adenine nucleotide translocator-3 polypeptide fused to a DLYDDDDK [SEQ ID NO:56] epitope tag.